REMARKS

Claims 15, 17-18, 20-23, 32-33 and 37, 39-42 are now in the case.

PRIORITY

The Specification was modified in accordance with 37 CFR 1.78(a) (2) by inserting a section entitled "Cross Reference to Related Applications" between the existing title and field of the invention sections referring to the PCT and Canadian prior applications from which the subject application claims priority benefit.

AMENDMENT TO THE CLAIMS

Reconsideration of this Application and entry of the foregoing amendments are requested. Claims 15, 17, 20, 37, 39 and 40 have been amended, claims 16, 19 and 38 have been cancelled and claims 41 and 42 have been added in view of the Office Action and to better define what the Applicants consider their invention, as fully supported by an enabling disclosure. Additional support for claims 15 and 37 may be found for instance at page 15, line 25 to page 16, line 2. The dependency of claim 39 was modified to depend from a non-canceled claim. Support for other modifications to the claims may be found in previously presented claims.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The Examiner rejects claims 15-23 and 32-33 and 37-40 under 35 U.S.C. § 112, second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner is of opinion that claims reciting the term "directly" are indefinite/unclear with regard to the candidate compound altering of resistance. She indicates that it is not clear what is meant by the term "directly".

What was intended by the recitation of the term "directly" was an emphasis on what the Applicants consider their invention, namely the showing that Annexin **contributes** to MDR. This is further explained below. Nevertheless, claims 15 and 37 were amended and while the wording "directly" was removed from the amended claims, this causality is now made implicit in the new formulation of these claims. The word "directly" was not meant to characterise the physical interaction between the candidate compound and Annexin.

The Examiner rejects claim 16 as indefinite because it appears to be of the same scope as claim 15. Claim 16 was deleted accordingly.

Claims 17 and 18 are rejected as being confusing. Claims 17 and 18 were reformulated accordingly.

Claims 17 and 20 remain rejected because the terminology "small molecule" is allegedly not specific as to the identity of the material proposed. The Applicants disagree as follows:

The references submitted in support of the response to the last Office Action were so provided simply to show that this term is a generic term that is well known in the art. Although the "small molecule" terminology is not defined in these references, all the "small molecules" that they refer to have one common trait: they are all non-peptides drug candidates. Applicants reiterate that this terminology is well known in the art and is always used to refer to non-peptides drug candidates. It is also submitted that the specification lists as non-limiting examples of compounds that may be identified by the present method as agonists and antagonists to Annexins with respect to their role in MDR include "nucleic acid molecules, peptides, antibodies, carbohydrates, or other pharmaceutical agents" (see page 15, line 25 to page 16, line 2). It is further respectfully submitted that a comparison of the elements of claim 17 with the above-cited list shows that the terminology "other pharmaceutical agents" which is not included *per se* in claim 17. It is submitted that the term "small molecule" which in accordance with the meaning of the person of ordinary skill in the art should be understood to be as encompassing as "other pharmaceutical agents" in the above-cited citation. Nevertheless, and to expedite prosecution, this terminology was removed from claims 17 and 20.

Claim 32 and other claims with the language "increase in the expression of an annexin protein, whereby said increased expression is capable of conferring MDR" are rejected because they appear indefinite in view of Applicants' statement in an earlier response that overexpression is not a reliable proof that the gene causes this phenotype. Applicants still agree with this statement: without any other indication clearly showing that Annexin's overexpression causes MDR, the concurrent observation of overexpression and MDR is not, in and of itself, sufficient to conclude that the former is a cause of the latter. This statement was used in support of Applicants' submission that the results presented in Wang are not enabling: they do not constitute sufficient proof

that Annexin contributes to MDR. Results presented in the present application however clearly prove that Annexin's overexpression is indeed a cause of the MDR resistance phenotype. It is therefore submitted that claims 32 and other claims containing this language do not contradict Applicants' earlier and present allegations.

Claims 19, 21-23, 33 and 38 are also rejected as indefinite as they depend on rejected claims. Claims 19 and 38 were cancelled. It is respectfully submitted that this objection should be removed in view of the above-presented arguments in support of the independent claims.

REJECTIONS UNDER 35 U.S.C. §102/103

Applicants gratefully note that the rejection of record under § 102(b) was withdrawn in favor of a 102/103 rejection. Applicant also gratefully note that claims 18 and 21-23 are free of the prior art.

The Examiner rejects claims 15-17, 19-20, 32, 33 and 37-40 under 35 U.S.C. § 102 (b)/103. She remains of the opinion that these claims are anticipated by Wang *et al.* ["Wang"] or, in the alternative, obvious over Wang. The applicant respectfully disagrees as follows:

The Examiner alleges that Table 1 of Wang demonstrates that P-40/Annexin I confers resistance to Taxol and Adriamycin. It is respectfully submitted that all that Table 1 shows is that Annexin I is overexpressed in cells resistant to these anticancer drugs. The Examiner further alleges that "the over expression of P-40 in paclitaxel or cis-platinum selected cell lines, in the absence of a detectable level of P-gp or MRP supports the notion that P-40 *may* confer resistance to cytotoxic drugs" and that " P-40 *could* modulate an MDR phenotype" and that "over expression *may* be important in the expression of the drug resistance phenotype" [emphasis added]. It is respectfully submitted that Wang does precisely that: it suggests that P-40 *may* confer resistance to cytotoxic drugs. It does not prove it, it simply provides incentive to pursue the research in that direction.

Applicants submit that in order to conclude that a reference anticipates or renders claims obvious, the reference should be sufficiently enabling to support claims similar to those that it is objected against. It is respectfully submitted that mere results of overexpression of Annexin in MDR cells would not be found sufficient to support claims directed to the function of Annexin, namely claims to method of screening for agonists or

antagonists to Annexin or to method of increasing or decreasing MDR by increasing or decreasing Annexin's expression. Applicants respectfully submit that for such claims, results such as those presented herein showing that 1) Annexin's over expression in MDR cells is due to Annexin mRNA and not to gene amplification (as is often the case in cells treated with anti-cancer drugs: they produce multiple copies of genes as a cell survival mechanism) (see Figure 3; Figure 3's legend at page 17, line 25 to page 18, line 7; page 27, line 14 to page 28, lines 2, and most particularly lines 23, 24 and 28-30 of page 27) and most importantly that 2) a cell that is sensitive to a cytotoxic drug that is transfected with a recombinant Annexin DNA (See Figures 6 to 9 and their legends at page 18, line 19 to 19, line 29; page 23, lines 8 to 28; and most particularly, page 29 line 6 to page 30, line 2; and page 33, lines 1 to 4) becomes resistant to this drug after transfection are necessary. Such results were necessary to show that Annexin is a cause of multidrug resistance.

Therefore, the Applicants disagree when the Examiner alleges that "one skilled in the art would be motivated to arrive at the claimed invention [...] because further investigation would lead to a direct correlation". It is reiterated that one skilled in the art would only be motivated to pursue the research in that direction. Wang itself, an inventor by definition more skilled than a person of ordinary skill in the art, admitted that that further investigations were needed to confirm the suggestion. It is also submitted that to conclude that claimed subject matter is obvious over a reference, with the knowledge provided by the reference, it should be possible to arrive to the subject matter without "undue experimentation".

Applicants submit that the experiments presented in the present application that support the finding that Annexin contributes to MDR, namely the transfection of cells with recombinant Annexin DNA and the characterization of the those transfected cells in particular of their behaviour when subjected to cytotoxic drugs. It is submitted that these results were the subject of a Ph.D. and took the work of two to five scientists during 5 years to obtain these results. It is therefore submitted that the quantity of experimentation that was required to come to the present invention following Wang's disclosure further shows that it was not obvious over that reference.

The Examiner also submits that Wang "discloses a method [for identifying] a protein that mediates drug resistance to anticancer drugs", that it "discloses a method that was used to isolate a monoclonal antibody (IPM96) which recognized a protein (P-

40) co-expressed with P-glycoprotein in several resistant cell lines", and that it "identifies a compound (P-40) that affects Annexin-based MDR in a cell in the presence of a drug and assessed the effect of the compound *as claimed in the present application*".

The Applicants have reformulated the claims in a way that more clearly shows how the present invention distinguishes itself from Wang. Indeed, the claims more clearly recite what the Applicants claim as their invention, namely the discovery that Annexin contributes to MDR. Now although Wang disclosed its attempts to find novel agonists of MDR, it did not disclose a method for identifying agonists or antagonists of Annexin.

CONCLUSIONS

The rejections of claims 15-23, 32, 33 and 37-40 are believed to have been overcome by the present remarks, and by the amendments to the claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such an action is earnestly solicited.

In the event that there are any questions concerning the Amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of the application may be expedited.

Authorization is hereby given to charge Deposit Account no. 17-0055 for any deficiencies or overages in connection with this Response.

Elias Georges *et al.*

Date: July 22, 2003 by

Jean C. BAKER
QUARLES & BRADY LLP
411 East Wisconsin Avenue
Milwaukee, WI 53202
Registration No. 35,433
(414) 277-5709

5443078.1